**Pharmacological mechanisms of the effect of Fufang Danshen on pain**

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**Fufang Danshen (FFDS) is a Chinese medicine formula which has been widely used in clinic for treatment of angina pectoris, coronary arteriosclerosis, hyperlipemia and Alzheimer’s disease. Although it has been proven to have effects on pain relief and antinociception, its pharmacological mechanisms remain to be elucidated. Current research performed methodologies of network pharmacology to investigate 223 targets for 35 compounds in FFDS. Statistics demonstrates that most compounds in FFDS conform to drug-likeness rules and have good bioavailability. Not only did active compounds and their targets in FFDS are identified, the pathways these compounds affect are also uncovered, which can be classified as signal transduction, endocrine system, nervous system and lipid metabolism. Relevance of FFDS and its herbs with pain has also been evaluated. These results provide a better understanding of FFDS in pain relief and may help to develop new analgesics.**

**Introduction**

Pain is a common symptom of many diseases like inflammation and cancer. As the improvement in quality of life, effective treatments of pain with few side effects are in great demand.

Fufang Danshen (FFDS), a Chinese herbal formula comprising Salvia miltiorrhizae (Danshen), Panax notoginseng (Sanqi) and Borneolum (Bing Pian), is clinically used for treatment of painful diseases like angina pectoris and Alzheimer’s disease. Although its function of pain relief has been revealed by many researchers, its mechanism remains unclear. In order to gain a better understanding of FFDS’s effects in attenuating pain and develop other analgesics, the study into pharmacological mechanisms of FFDS is imperative.

Network pharmacology is a recently developed approach in drug discovery based on systems biology. Different from the concept that a drug acts as a selective ‘key’ that fits into the ‘lock’ of a specific drug target, network pharmacology studies how drugs function in a network consisting of several nodes or targets, therefore has become a powerful tool for discovering drugs of relatively complex diseases and minimizing side effects [2]. Recently, this method was utilized by Y T Sun and J Yang to identify active ingredients and targets in FFDS.

**Recent Progress**

Y T Sun and J Yang first assessed the relevance of FFDS and its herbs with pain by literature mining. The P-values of FFDS, Salvia miltiorrhizae, Panax notoginseng and Borneolum are calculated separately, which demonstrate that the three ingedients of FFDS and FFDS itself are all relavent to pain, among which Salvia miltiorrhizae is the best studied one.

The target numbers of 35 compounds in FFDS are then counted. Panax notoginseng turned out to have the most targets with a number of 143. The second highest targets number is 99 for Salvia miltiorrhizae, while only 17 targets belong to Borneolum. The targets number of a certain herb consists with its role and importance in pain relief process, which means Panax notoginseng and Salvia miltiorrhizae are major herbs in FFDS.

The cooperativity of three herbs are also studied by counting the number of targets shared by two or three herbs. Borneolum is necessary for the pain-relieving effect as well because of 5 targets belonging to only itself and 12 targets shared with Salvia miltiorrhizae or Panax notoginseng. The targets of only Salvia miltiorrhizae or Panax notoginseng are found to be involved in pathways enriched by targets of the opposite herb only.

The properties of 217 compounds in FFDS were tested in order to measure their drug-likeness. As a result, 173 compounds conform to Lipinski's rule of five (i.e. molecules with a molecular mass less than 500 Da, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and an octanol–water partition coefficient log P not greater than 5 is likely to be drugs [3]). Statistics also reveals that 76.5% of ingredients in FFDS have good bioavailability.

Based on the results of the ingredients and targets of FFDS, scientists subsequently analyzed the pathways in which those targets are involved. Calculation of P-values of each pathway shows its relevance with pain. As a result, 26 pathways are found to be relevant to pain, which can be classified into different categories. Pathways in signal transduction are the most, consisting with the fact that the generation and conduction of pain need the function of nervous system, during which signal is passed between neurons and through nerves. Besides, other pathways like the endocrine system and lipid metabolism also play an essential role in painful conditions.

The difference between disease proteins and therapeutic targets are highlighted in [1]. Disease proteins are encoded by disease genes, serving as the cause of diseases. Therapeutic targets, however, are factors crucial in curing diseases. After the study of those therapeutic targets of FFDS, scientists then paid attention to FFDS-related pain disease proteins (i.e. pain disease proteins that can be directly or indirectly targeted by FFDS). 56 FFDS-related pain disease proteins were finally identified.

Comparison between targets of FFDS and other drugs known for pain relief uncovered targets shared by many pain relief drugs. For example, the Mu-type opioid receptor (OPRM1) is targeted by 55 drugs, and PTGS2 is targeted by 14 drugs.

Based on the essential protein theory, which suggests that a highly connected protein plays a significant role in a network, researchers evaluate the degrees of FFDS targets, among which JUN, Myc proto-oncogene protein (MYC) and VCAM1 have relatively higher degrees.

**Discussion**

Network pharmacology has been proven to be a powerful tool in the study of traditional Chinese medicine for it provides effective methods for identification of active ingredients and evaluation of drug targets. With the help of network pharmacology, Y T Sun and J Yang made noticeable contributions to the study of pharmacology mechanisms of FFDS. They not only assessed the relevance between FFDS and pain, confirm the drug-likeness and bioavailability of FFDS, but also counted the targets affected by FFDS and FFDS-related pain disease proteins, analyzed the pathways involved, evaluated the significance of targets and subsequently compared FFDS with other pain drugs. These works allow us to have a better understanding of the efficacy of FFDS in pain relief and serve as a guideline in the design of new pain-relieving drugs.

**References**

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